Remarks

Claims 1, 3-7, 9-12, 17, 19-21, 23, 24, 36-38, 41-58, 61, 63, 69, 71-73, 76, 81, 96 and 100-104 were pending in the application. No claims are canceled or added. Thus, upon entry of this amendment, **claims 1, 3-7, 9-12, 17, 19-21, 23, 24, 36-38, 41-58, 61, 63, 69, 71-73, 76, 81, 96 and 100-104 will be pending**; of these, claims 7, 9, 10, 12, 20, 21, 36, 37, 42-44, 46-58, 61, 63, 69, 71-73, 76, 81 and 101 are withdrawn.

Support for the recitation of physiological salt concentration in claim 1 can be found throughout the specification, for example, paragraph [0042] and Examples 2-4 and 8-10 (physiological salt concentration is also known as ionic strength).

Support for the amendment to claim 102 can be found in paragraph [0043].

Claims 103-104 are amended to depend from claim 1.

SUMMARY OF TELEPHONE INTERVIEW WITH EXAMINER

Applicants thank Examiners Ha and Kam for the courtesy of a telephone interview on October 7, 2008 with Applicants' representatives Sheree Lynn Rybak and Lisa Brown and inventor Amalia Aggeli. During this interview, the 35 U.S.C. § 102(b) rejection was discussed. Inventor Aggeli (and co-author of the reference cited in the 102 rejection), explained how the cited reference and the claims differ. Dr. Aggli explained that in the cited reference peptide 11-3 when present in water at neutral pH is in a monomeric state and not a gel (it is in solution), and at pH 2 it self-assembles into beta tapes and forms a gel. But as disclosed in the patent application, when peptide 11-3 (or other peptides with net +2 or -2 charge) is present in physiological salt and pH conditions, the peptide forms a gel. It was recommended that claim 1 further recite physiological salt concentrations.

REJECTION UNDER 35 U.S.C. §102

Claims 1, 3-6, 11, 17, 19, 23, 24, 38, 41, 96, 100 and 102-104 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Aggeli *et al.* (*Peptide Science – Present and Future*, 1999, 30-33). Applicants disagree and request reconsideration.

As recited herein, claim 1 is directed to a material comprising ribbons, fibrils or fibres, wherein each of the ribbons, fibrils or fibres has an antiparallel arrangement of peptides in a β-sheet tape-like substructure *at physiological pH and physiological salt concentrations*, wherein each peptide comprises a net -2 or a +2 charge, and wherein the peptides are selected from P11-3 and P11-5. The remainder of the rejected claims depend directly or indirectly from claim 1.

In contrast to the pending claims, Aggeli *et al.* teach that a peptide having the amino acid sequence of P11-3 (referred to in Aggeli *et al.* as DN1-2E) *when in water* is only capable of forming a β-sheet tape-like structure at pH 4 or less. In fact, Aggeli *et al.* teach that this peptide *when in water* is a *fluid* (in solution) at physiologic pH (Figure 2 of Aggeli *et al.*). Thus, based on the teachings of Aggeli *et al.*, one of skill in the art would not have recognized that a peptide having the amino acid sequence of P11-3 (or P11-5) would form a β-sheet structure at physiological pH and salt conditions as instantly claimed. Thus in Aggeli *et al.* the peptide was exposed to water, not to physiological pH and salt conditions. The phosphate buffer referenced on pages 5-7 of the Office action and in Figure 3 of Aggeli *et al.* does not provide physiological salt conditions. There is no NaCl present. The phosphate buffer has sodium phosphate but not sodium chloride. Thus the ionic strength of the buffer described in Figure 3 of Aggeli *et al.* is not physiological. The peptide is in a solution of 10 mM sodium phosphate in pure water (there is nothing else in this solution apart from peptide, pure water and 10 mM sodium phosphate; therefore this is not a physiological solution in terms of the salt, and salt concentration present in it). As described in Aggeli *et al.*, under this condition, the peptide was found to be monomeric random coil and to form Newtonian fluid solution. Thus the observations disclosed in Aggeli *et al.* do not teach anything regarding the self-assembling and gelling behavior of the peptide in physiological pH and physiological salt concentration, which is the subject of the pending claims.

Claim 1 is amended to clarify that the peptide forms ribbons, fibrils or fibres at physiological pH and salt concentrations. One skilled in the art will appreciate that there is a modest range of pH and salt values considered to be physiological. For example, the absolute values may vary depending on the organism or the particular fluid. As shown in Exhibit A (Dawson RMC, Elliot DC, Elliot WH and Jones KM, Data for Biochemical Research, second edition, Oxford press 1969, first edition 1959) the added amount of NaCl in Ringers solutions (to

be isotonic with serum) may vary depending upon the other Na and Cl containing salts added. Exhibit B (Eckert, R., Randall, D., and Augustine, G., Animal Physiology: Mechanisms and Adaptations, Third Edition, 1988, page 390) in Table 12-3 shows exemplary physiological salt concentrations from various body fluids. Exhibit C (Lehninger, Biochemistry, Second edition) in Table 2-6 lists the physiological pH of blood serum and other body fluids. Exhibit D (Haskal, *J. Amer. Acad. Nurse Pract.* 19:563-79, 2007) on page 565 states that a normal blood sodium level is 135 - 146 milliEquivalents/liter (mEq/L), or in international units, 135 - 146 millimoles/liter (mmol/L).

Thus, because Aggeli *et al.* do not teach each and every limitation of the pending claims, the claims are not anticipated. Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C. §102(b).

CONSIDERATION OF ADDITOINAL SPECIES

As generic claim 1 is in condition for allowance, Applicants request that additional species be examined at this time, pursuant to 37 C.F.R. § 1.141.

CONCLUDING STATEMENT

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the undersigned to discuss any outstanding matters.

Respectfully submitted,

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By /Sheree Lynn Rybak/
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al volatile buffer mixtures

pH	*Constituents*
1·9	CH_3COOH (87 ml glacial), HCOOH (25 ml 88%) to 1 l with H_2O
2·1	HCOOH (25 ml 88%) to 1 l with H_2O
3·1	Pyridine (5 ml), CH_3COOH (100 ml glacial) to 1 l with H_2O
3·5	Pyridine (5 ml), CH_3COOH (50 ml glacial) to 1 l with H_2O
4·7	Pyridine (25 ml), CH_3COOH (25 ml glacial) to 1 l with H_2O
6·5	Pyridine (100 ml), CH_3COOH (4 ml glacial) to 1 l with H_2O
7·9	0·03M-NH_4HCO_3
8·9	$(NH_4)_2CO_3$ (20 g/l solution)

'ROXIMATE pH OF SOME COMMON REAGENTS ROOM TEMPERATURE

from R. G. Bates, *Determination of* pH: *Theory and Practice*, 2nd ed., Wiley, York (1964))

Substance	*Molarity*	pH
Acid benzoic	Saturated	2·8
Acid boric	0·1	5·3
Acid citric	0·1	2·1
Acid hydrochloric	0·1	1·1
Acid oxalic	0·1	1·3
Acid salicylic	Saturated	2·4
Acid succinic	0·1	2·7
Acid tartaric	0·1	2·0
Acid trichloroacetic	0·1	1·2
Alum, ammonium	0·05	4·6
Alum, potassium	0·1	4·2
Ammonia water	0·1	11·3
Ammonium chloride	0·1	4·6
Ammonium oxalate	0·1	6·4
Ammonium phosphate, primary	0·1	4·0
Ammonium phosphate, secondary	0·1	7·9
Ammonium sulphate	0·1	5·5
Barbital sodium	0·1	9·4
Borax	0·1	9·2
Calcium hydroxide	Saturated	12·4
Potassium acetate	0·1	9·7
Potassium bicarbonate	0·1	8·2
Potassium bioxalate	0·1	2·7
Potassium carbonate	0·1	11·5
Potassium phosphate, primary	0·1	4·5
Sodium acetate	0·1	8·9
Sodium benzoate	0·1	8·0
Sodium bicarbonate	0·1	8·3
Sodium bisulphate	0·1	1·4
Sodium carbonate	0·1	11·5
Sodium hydroxide	0·1	12·9
Sodium phosphate, primary	0·1	4·5
Sodium phosphate, secondary	0·1	9·2

PHYSIOLOGICAL MEDIA

Krebs mammalian Ringer solutions

Parts by volume

Solutions required (all approximately isotonic with serum)	*Krebs–Henseleit original Ringer bicarbonate*† *A*	*Krebs original Ringer phosphate B*	*Krebs improved Ringer I*† *C*	*Krebs improved Ringer II D*	*Krebs improved Ringer III E*	*Krebs substrate fortified serum*†
0·90% NaCl (0·154M)	100	100	80	83	95	100 vol. serum prepared from rapidly cooled blood
1·15% KCl (0·154M)	4	4	4	4	4	
1·22% $CaCl_2$ (0·11M)	3‡	3‡	3‡		3‡	
2·11% KH_2PO_4 (0·154M)	1	1	1	1	1	
3·8% $MgSO_4 \cdot 7H_2O$ (0·154M)	1§	1§	1§	1§	1§	
1·3% $NaHCO_3$	21‖		21‖	3	3	
0·1M-Phosphate buffer pH 7·4 (17·8 g $Na_2HPO_4 \cdot 2H_2O$ + 20 ml N-HCl diluted to 1 l)		21				
0·16M-Na pyruvate (or L-lactate)			4	4	4	3
0·1M-Na fumarate			7	7	7	6
0·16M-Na-L-glutamate			4	4	4	3
0·3M-(5·4%) glucose			5	5	5	5
0·1M-Na phosphate buffer [100 vol. 0·1M-Na_2HPO_4 (1·78% $Na_2HPO_4 \cdot 2H_2O$) + 25 vol. 0·1M-NaH_2PO_4 (1·38% $NaH_2PO_4 \cdot H_2O$)]				18	3	

† Gassed with 5% CO_2 in gas phase.
‡ Twice the conc. of ionized Ca in serum (*Nature, Lond.* **184**, 1315 (1959)).
§ For human serum-substitute replace 50% with 0·154M-$MgCl_2$.
‖ Gassed with 100% CO_2 for 1 hr before mixing with other solutions.

Notes. A and *B. Krebs and Henseleit bicarbonate and phosphate Ringer* (*Z.P.C.* **210**, 33 (1932); **217**, 193 (1933)). Cl^- ions about 20 per cent higher than in mammalian serum.

C. Krebs improved Ringer I (*B.B.A.* **4**, 249 (1950)). Conc. of electrolytes and organic acids similar to mammalian serum, and contains intrinsic substrate.

D. Krebs improved Ringer II. Low bicarbonate, Ca^{++} free (*B.B.A.* **4**, 249 (1950)). Suitable for measurement of CO_2 production by direct CO_2 absorption. Valuable for minced tissues and homogenates as higher and steadier rates of respiration obtained in Ca-free media. Concentration of phosphate is 20 times higher and bicarbonate 10 times lower than physiological.

E. Krebs improved Ringer III. Low phosphate, bicarbonate, and CO_2. Suitable for measurement of CO_2 production by direct CO_2 absorption. Concentration of Ca about twice that of the ionized Ca of serum. Limited buffering capacity.

Storage. A composite solution containing the NaCl, KCl, $CaCl_2$, KH_2PO_4, and $MgSO_4$ ± 3 vols. $NaHCO_3$ solution will not precipitate Ca or Mg. The danger of microfloral contamination is avoided if the *individual* solutions are made up at five times the required concentrations and diluted before use. Solutions of organic acid salts and glucose should be sterilized, frozen, or freshly prepared.

Other Ringer solutions

The following salts and glucose are dissolved in water to produce 100 ml solution. Solutions containing $NaHCO_3$ should not be sterilized by heating since the loss of CO_2 causes a more alkaline reaction. They may be sterilized by filtration through a Seitz, Berkefeld or similar filter.

	Ringer (frog heart) (g)	*Locke† (mammalian heart)* (g)	*Tyrode‡ (rabbit intestine)* (g)	*Amphibian Ringer* (g)	*Marine mollusc saline* (g)	*Marine crustacea saline* (g)	*Elasmobranch saline* (g)
NaCl	0·65	0·9§	0·8	0·65	2·34	2·92	1·64
KCl	0·014	0·042	0·02	0·025		0·075	0·089
$CaCl_2$ (anhyd.)	0·012	0·024	0·02	0·03	0·56	0·44	0·11
$MgCl_2$ (anhyd.)			0·01‖		0·76		
$NaHCO_3$	0·02	0·01–0·03	0·1	0·02 (pH 7·0–7·4)			0·038
NaH_2PO_4 (anhyd.)	0·001		0·005				0·006
Glucose	0·2	0·1–0·25	0·1				0·1
Urea							2·16

† Locke, *Zentbl. Physiol.* **14**, 670 (1900).
‡ Tyrode, *Arch. int. Pharmacodyn. Thér.* **20**, 205 (1910).
§ For cold-blooded animals reduce NaCl to 0·65 g.
‖ Pernow, *Acta physiol. scand.* **29**, Suppl. 105 (1953), uses $MgCl_2 \cdot 6H_2O$.

Artificial sea water

(i) Prepared from solutions isotonic with sea water. Atlantic sea water is 3·50–3·55% saline while North Sea sea water is 3·4–3·5%.

		ml
0·54M	NaCl	739·6
0·54M	KCl	18·05
0·36M	$MgCl_2$	145·7
0·36M	$CaCl_2$	28·0
0·44M	Na_2SO_4	63·0
0·54M	$NaHCO_3$	4·6
0·54M	NaBr	1·05 (for most purposes NaCl can be substituted)

(ii) Prepared from the following salts dissolved in water and diluted to 1 litre. 24·7 g NaCl; 0·7 g KCl; 6·3 g $MgSO_4 \cdot 7H_2O$; 4·6 g $MgCl_2 \cdot 6H_2O$; 1·0 g anhyd. $CaCl_2$; 0·2 g $NaHCO_3$.

21. Methods for the Detection of Biochemical Compounds on Paper and Thin Layer Chromatograms, with some notes on separation

TABLE 12-3 Electrolyte composition of the human body fluids

Electrolytes	Serum (meq/kg H_2O)	Interstitial fluid (meq/kg H_2O)	Intracellular fluid* (meq/kg H_2O)
Cations			
Na^+	142	145	10
K^+	4	4	156
Ca^{++}	5		3
Mg^{++}	2		26
Totals	153	149	195
Anions			
Cl^-	104	114	2
HCO_3^-	27	31	8
$HPO_4^=$	2		95
$SO_4^=$	1		20
Organic acids	6		
Protein	13		56
Totals	153	145	190

Note: Some of the ions contained within cells are not entirely dissolved in the cytoplasm, but may also be sequestered within cytoplasmic organelles. Thus, the true free Ca^{++} concentration in the extracellular is typically less than 10 $^{-7}$ meq/kg H_2O rather than the overall value given in the table. Equality of anion and cation totals to agree with electroneutrality.

because the skin in amphibians is generally more permeable than that in the other vertebrate classes. The camel is faced with a rather different set of problems. In the face of a limited water supply, it must make important compromises: On the one hand, it must conserve water but also eliminate toxic end products of metabolism, such as urea; on the other hand, it must regulate the salt concentrations of its extracellular fluids as it loses water through evaporation that is either unavoidable or is necessary to prevent overheating.

The osmotic exchanges that take place between an animal and its environment can be divided into two classes (Figure 12-3): (1) *obligatory exchanges*—namely, those that occur mainly in response to physical factors over which the animal has little or no physiological control; and (2) *regulated exchanges*, which, as the name indicates, are physiologically controlled and serve to aid in maintaining internal homeostasis. Regulated exchanges generally serve to compensate for the obligatory exchange.

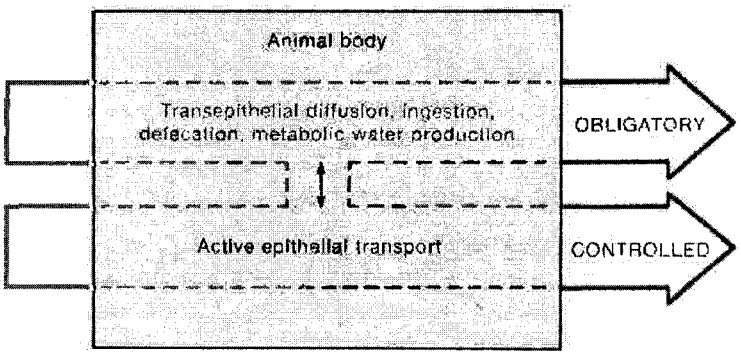
In Equation 4-3 it is seen that the flux of a substance across a membrane is determined by its concentration gradient, the surface area of the membrane involved, and the permeability of the membrane. The same factors influence the obligatory exchange of substances across an epithelium. In considering obligatory exchange between an organism and its environments, the integument, respiratory surfaces, and other epithelia in contact with the surrounding milieu act as the barrier to obligatory exchange. The various factors that contribute to the obligatory exchange have been reviewed by Bentley (1971), and are outlined next.

Factors Influencing Obligatory Exchange

1. *Gradients between the extracellular compartment and the environment.* The greater the difference between the concentration of a substance in the external medium and that in the body fluids, the greater the tendency for net diffusion in the direction of low concentration. Thus, although a frog immersed in a pond tends to take up water from its hypotonic environment, a bony fish in seawater is faced with the problem of losing water into the hypertonic seawater.

2. *Surface-to-volume ratio.* The volume of an animal varies with the cube of its linear dimensions, whereas its surface area varies with the square of its linear dimensions. That is, the surface-to-volume ratio is greater for small animals than for large animals. It follows that the surface area of the integument, through which water or a solute can exchange with the environment, is greater relative to the water content of a small animal than for a large animal. This means that for a given net rate of exchange across the integument (in moles per second per square centimeter), a small animal will dehydrate (Figure 12-4) or hydrate more rapidly than a larger animal of the same shape.

3. *Permeability of the integument.* The integument as a barrier between the extracellular compartment and the environment. The permeability of the integument to water and solutes varies with animal groups



12-3 Two major classes of osmotic exch... between an animal and its environment. ... tory exchanges are those that occur in ... sponse to physical factors over which th... animal has little short-term physiological ... trol. Controlled exchanges are those that ... animal can vary physiologically to maint... ternal homeostasis. Substances entering ... animal by either path can leave by the ... path.

BIOCHEMISTRY

SECOND EDITION

THE MOLECULAR BASIS

OF CELL STRUCTURE AND FUNCTION

ALBERT L. LEHNINGER

THE JOHNS HOPKINS UNIVERSITY

SCHOOL OF MEDICINE

WORTH PUBLISHERS, INC.

on pure distilled water. Since the concentration of water in pure water is very high (it is equal to the number of grams of H_2O in a liter divided by the gram molecular weight of water, or 1,000/18 = 55.5 *M*) and since the concentrations of H^+ and OH^- ions are very low in comparison (1×10^{-7} *M* at 25°C), the molar concentration of water is not significantly changed by its very slight ionization. The equilibrium-constant expression may thus be simplified to

$$55.5K_{eq} = [H^+][OH^-]$$

and the term $55.5K_{eq}$ can then be replaced by a lumped constant K_w, called the ion product of water,

$$K_w = [H^+][OH^-]$$

The value of K_w at 25°C is 1.0×10^{-14}. In an acid solution, the H^+ concentration is relatively high and the OH^- concentration correspondingly low; in a basic solution, the situation is reversed.

K_w, the ion product of water, is the basis for the pH scale (Table 2-5), a means of designating the actual concentration of H^+ (and thus of OH^-) ions in any aqueous solution in the acidity range between 1.0 *M* H^+ and 1.0 *M* OH^-. The pH scale was devised by the Danish biochemist S. P. L. Sørensen as a means of avoiding cumbersome numbers like 0.0000001 or 1.0×10^{-7} to express the low hydrogen-ion concentrations in biological fluids. He defined the term pH as

$$pH = \log_{10} \frac{1}{[H^+]} = -\log_{10} [H^+]$$

In a precisely neutral solution at 25°C

$$[H^+] = [OH^-] = 1.0 \times 10^{-7} M$$

The pH of such a solution is

$$pH = \log \frac{1}{1 \times 10^{-7}} = 7.0$$

The value of 7.0 for the pH of a precisely neutral solution is thus not an arbitrarily chosen figure; it is derived from the absolute value of the ion product of water at 25°C. It is important to note that the higher the pH number, the lower the hydrogen-ion concentration, and vice versa. Note that the pH scale is logarithmic, not arithmetic. To say that two solutions differ in pH by 1 pH unit means only that one solution has 10 times the hydrogen-ion concentration of the other. Table 2-6 lists the pH of some fluids.

Table 2-5 The pH scale

$[H^+]$, *M*	pH	$[OH^-]$, M
1.0	0	10^{-14}
0.1	1	10^{-13}
0.01	2	10^{-12}
0.001	3	10^{-11}
0.0001	4	10^{-10}
0.00001	5	10^{-9}
10^{-6}	6	10^{-8}
10^{-7}	7	10^{-7}
10^{-8}	8	10^{-6}
10^{-9}	9	10^{-5}
10^{-10}	10	10^{-4}
10^{-11}	11	0.001
10^{-12}	12	0.01
10^{-13}	13	0.1
10^{-14}	14	1.0

Table 2-6 pH of some fluids

Fluid	pH
Seawater (varies)	7.5
Blood plasma	7.4
Interstitial fluid	7.4
Intracellular fluids	
Muscle	6.1
Liver	6.9
Gastric juice	1.2–3.0
Pancreatic juice	7.8–8.0
Saliva	6.35–6.8
Cow's milk	6.6
Urine	5–8
Tomato juice	4.3
Grapefruit juice	3.2
Soft drink (cola)	2.8
Lemon juice	2.3

Measurement of pH

Measurement of pH is one of the most common and useful analytical procedures in biochemistry since the pH deter-

American Academy of Nurse Practitioners

PRACTICE

Current issues for nurse practitioners: Hyponatremia

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Keywords
Hyponatremia; arginine vasopressin; SIADH; AVP receptor antagonists; conivaptan.

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Abstract

Purpose: To review the assessment, diagnosis, and management of hyponatremia (serum sodium <135 mEq/L), the most common electrolyte disturbance as a result of dysregulation of water balance in hospitalized or institutionalized patients.

Data sources: Comprehensive search using keywords AVP receptor antagonists, hyponatremia, SIADH, conivaptan, tolvaptan, lixivaptan, nurse practitioner, and others was carried out using the National Library of Medicine (PubMed) Web site from which full-text articles were obtained. Meeting abstracts were obtained from scientific sessions including the American Society of Nephrology Renal Week 2004 and the Endocrine Society's 87th Annual Meeting (2005). The Vaprisol (conivaptan hydrochloride injection) package insert was referenced and obtained from FDA.gov.

Conclusions: A diagnosis of hyponatremia requires thorough investigation for underlying causes and prompt treatment to prevent poor patient outcomes. In clinical trials, a new class of drugs called the arginine vasopressin (AVP) receptor antagonists or aquaretics has been shown to be safe and effective for the treatment of hyponatremia. Among this class of agents, intravenous conivaptan hydrochloride, indicated for the treatment of euvolemic hyponatremia in hospitalized patients, is the first drug in class approved for use.

Implications for practice: Elderly patients, and those with certain conditions such as heart failure, tuberculosis, cirrhosis, and head injury, may be at increased risk for hyponatremia. In hospitalized patients following surgery and the use of certain medications, hyponatremia is a common condition. A thorough understanding of the physiology of water balance and the risk factors associated with hyponatremia is essential for prompt and effective intervention. Awareness of the limitations of conventional therapies and the availability of new treatment options for hyponatremia allows clinicians to optimize patient care.

Introduction

Reported in up to 28% of patients undergoing acute hospital care and 21% of patients undergoing ambulatory care (Hawkins, 2003), hyponatremia (generally defined as a serum sodium concentration <135 mEq/L) is one of the most common electrolyte disorders in clinical medicine (Arieff, 1986; Beers & Berkow, 1999; Verbalis, 1993; Wong & Verbalis, 2002). Severe acute hyponatremia, if unrecognized and untreated, can cause irreversible neurological damage or even death. Chronic hyponatremia may lead to severe neurological sequelae if its treatment rate is overly rapid (Arieff; Sterns, Cappuccio, Silver, & Cohen, 1994; Verbalis, 2003). In fact, rapid reversal of the sodium deficit in both acute and chronic hyponatremia may result in the neurological disorder known as osmotic demyelination syndrome (ODS) (Verbalis, 1993).

Successful management of hyponatremia requires careful assessment, accurate diagnosis, and an integrated team approach, and nurse practitioners (NPs) play an increasingly important role in the recognition of risk factors and the management of hyponatremia. Signs and symptoms of

hyponatremia are nonspecific but may lead to a precipitous decline in patient well-being, and many of the conventional treatment options for hyponatremia have proved to be suboptimal (Goldsmith & Gheorghiade, 2005). Use of these conventional treatments may be limited by variable efficacy, slow onset of action, patient compliance issues, and toxicities (Goldsmith & Gheorghiade; Wong & Verbalis, 2001). A new class of agents, the arginine vasopressin (AVP) receptor antagonists, has been developed for the treatment of hyponatremia. Note that AVP was formerly known as ADH (antidiuretic hormone). One agent in this class, intravenous (IV) conivaptan hydrochloride, has been approved for the treatment of euvolemic hyponatremia in hospitalized patients ("Vaprisol PI," 2006).

This article will discuss the assessment and management of the patient with hyponatremia for NPs. Background information on the science of normal body fluid homeostasis and the pathophysiology of hyponatremia will be presented first. The efficacy and safety data from clinical trials of AVP receptor antagonists including IV conivaptan and oral formulations of lixivaptan and tolvaptan will also be presented.

Normal physiology of water balance

In adult humans, total body weight (based on an average 70-kg [154-lb] male) consists of 55%–65% water (Berl & Verbalis, 2004). Intracellular fluid accounts for slightly less than two thirds of total body water (TBW), and extracellular fluid (ECF) accounts for slightly more than one third of TBW. Of the ECF, roughly 75% is interstitial fluid and 25% intravascular fluid, or blood (Figure 1) (Berl & Verbalis; Marieb, 2004). In the body, water and sodium homeostasis consists of the interaction between body water, the primary determinant of ECF, and sodium, a primary and vital constituent in cellular metabolism (Verbalis, 2003). Defined as the concentration of all solutes in a given weight of water, osmolality can be calculated as (Verbalis):

$$P_{Osm}(\text{mOsm/kg water}) = 2 \times (\text{serum sodium}) + \text{glucose} + \text{BUN}$$

P_{Osm} = plasma osmolality(in Système International d'unités)

Serum sodium, glucose, and blood urea nitrogen (BUN) are measured in mmol/L.

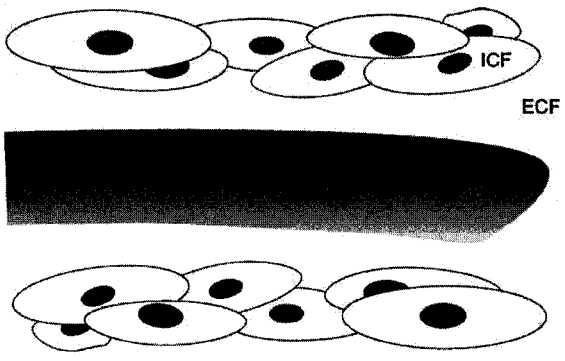

Figure 1 Fluid compartments—cellular level. Intracellular fluid accounts for slightly less than two thirds of TBW, and ECF accounts for slightly more than one third of TBW. Of the ECF, roughly 75% is interstitial fluid and 25% intravascular fluid, or blood (Berl & Verbalis, 2004; Marieb, 2004). Adapted with permission from Marieb (2004).

Water metabolism

The two main mechanisms in the human body that regulate and maintain body water homeostasis include thirst (prompting fluid intake) and excretion of body water via the collecting ducts of the kidneys (promoting fluid output) (Verbalis, 2003). Thirst may be stimulated by osmotic changes in the ECF, and studies have shown that an increase of only 1%–4% of plasma osmolality stimulates thirst in humans (Verbalis). Animal models have shown that thirst is also stimulated by a decrease in ECF volume; however, decreases in blood volume of 4%–15% are required in animals to stimulate drinking behavior (Verbalis). Although osmotic thirst is a sensitive measure, the homeostasis of body water is more significantly regulated via urinary excretion (diuresis) or retention (antidiuresis) in the kidneys. AVP, a hormone secreted into circulation from the posterior pituitary, acts upon the AVP receptors in the collecting ducts to regulate urinary flow (Verbalis).

Aquaporins and aquaresis

AVP stimulates water retention by interacting with V_2 receptors in the kidney, causing insertion of aquaporin-2 (AQP-2) water channels into the apical membranes of the principal cells of the renal collecting tubule (Verbalis, 2003). The interaction of circulating AVP with renal V_2 receptors stimulates release of adenylate cyclase, which activates intracellular cyclic adenosine monophosphate (cAMP) as a secondary messenger. The activation of intracellular cAMP causes the migration of the AQP-2 protein from intracellular vesicles to the plasma membranes of the cells of the renal collecting ducts, creating water-permeable pores and thus increasing the water permeability of the renal collecting tubules (Ferguson, Therapondos, Newby, & Hayes, 2003; Nielsen, 2002). Increased water reabsorption in the collecting ducts results in a decreased flow of urine (antidiuresis) and an increased urinary solute

concentration. Antidiuresis is the primary means by which the body maintains fluid volume and plasma osmolality (Verbalis).

Sodium physiology

Serum sodium is maintained within narrow limits (135–146 mEq/L) by several mechanisms. The two most important mechanisms are the glomerular filtration rate (GFR), which affects the number of sodium ions that pass from the glomerular capillaries into Bowman's capsule and the renal tubules, and the release of aldosterone by the adrenal glands, which increases the reabsorption of sodium by the distal nephron (Verbalis, 2003). The renal reabsorption and elimination of water are illustrated in Figure 2 (Costello-Boerrigter, Boerrigter, & Burnett, 2003).

Hyponatremia: Classification by volume status

Dysregulation of body fluid homeostasis may be caused by alterations in ECF osmolality and are generally classified under hypoosmolar (decreased solute compared with TBW) or hyperosmolar (excess solute compared with TBW) disorders (Verbalis, 2003). A disorder of hypoosmolality, hyponatremia can be further subclassified by volume status (Table 1) (Baylis, 2003).

ECF volume and hyponatremia

Hyponatremia, an excess of body water relative to extracellular sodium, may be caused either by the excessive loss of sodium (depletional hyponatremia) or by the excessive retention of water (dilutional hyponatremia) (Verbalis, 2003). Depletional hyponatremia is usually associated with decreased ECF volume (hypovolemic hyponatremia), which may be caused by disorders or medications that produce excessive renal salt loss (e.g., diuretic use or renal salt-wasting syndrome). Dilutional hyponatremia is most often associated with elevated total ECF volume with or without clinical evidence of edema (hypervolemic hyponatremia). Essentially, normal ECF volume is considered euvolemic hyponatremia (Verbalis).

Patients frequently develop *hypovolemic hyponatremia* as a result of extrarenal sodium loss because of diarrhea and vomiting (Coenraad et al., 2003). *Hypervolemic hyponatremia* is usually caused by fluid overload associated with elevated AVP secretion, which can be found in liver cirrhosis, renal disease, and congestive heart failure (CHF)

Table 1 Types of hyponatremia[a]

ECF status	Mechanisms	Associated clinical conditions
Hypervolemic (dilutional)	EC sodium increased, TBW greatly increased	CHF, cirrhosis, nephrotic syndrome, acute kidney failure
Euvolemic (dilutional)	EC sodium normal, TBW slightly increased	SIADH, thiazide diuretic use, oral hypoglycemic drug use
Hypovolemic (depletional)	EC sodium decreased, TBW slightly decreased	Diuretic use, salt-wasting nephropathy, vomiting, diarrhea, burns

Note. EC, extracellular.
[a]Adapted from Baylis (2003) with permission from Elsevier.

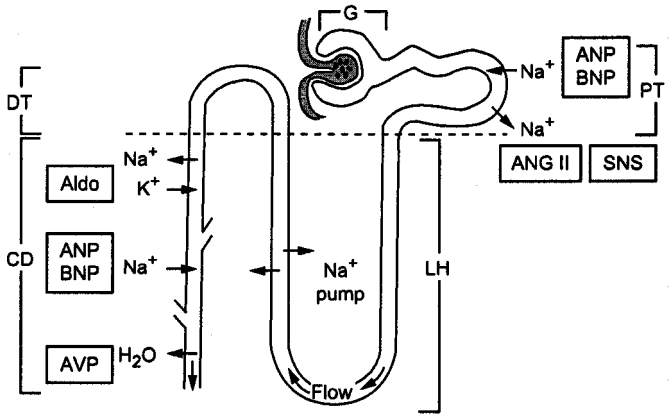

Figure 2 Collecting duct and other main segments of the nephron, with major sites of physiological regulation.
Note. Aldo, aldosterone; ANG II, angiotensin II; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CD, collecting duct; DT, distal tubule; G, glomerulus; LH, loop of Henle; PT, proximal tubule; SNS, sympathetic nervous system. Reprinted from Costello-Boerrigter et al. (2003) with permission from Elsevier.

(Verbalis, 2003). *Euvolemic hyponatremia* is usually caused by the elevated release of AVP and is most commonly associated with the syndrome of inappropriate antidiuretic hormone (SIADH) (Table 1) (Baylis, 2003; Miller, 2001; Verbalis, 2003; Wong & Verbalis, 2002).

Laboratory values

Normal laboratory values for serum sodium and osmolality, urine sodium and osmolality, and normal values for other laboratory tests commonly used in the examination of patients with hyponatremia are listed in Table 2, in addition to the abnormal laboratory values typically seen in those with hyponatremia and SIADH (Beers & Berkow, 1999; Boh, 2001; Verbalis, 2003).

Arginine vasopressin

AVP is released from the posterior pituitary in response to decreases in circulating plasma osmolality (detected by hypothalamic osmoreceptors) and/or blood volume or pressure (detected by vascular baroreceptors) (Costello-Boerrigter et al., 2003; Freda, Davidson, & Hall, 2004; Verbalis, 2003). In the volume-regulatory system of salt and water balance, the normal physiological response to fluid load and depletion is initiated at the sensor level. Baroreceptors in the atria are stretched during fluid overload, activating the release of atrial natriuretic peptide and brain natriuretic peptide (BNP), which leads to increased excretion of sodium and water from the kidneys. Circulatory volume depletion causes activation of the baroreceptors in the aorta, carotid arteries, and kidneys, leading to secretion of AVP and activation of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system mechanisms, which in turn causes sodium and water retention at the level of the kidneys (Costello-Boerrigter et al.).

AVP receptor subtypes: V_2, V_{1A}, and V_{1B}

AVP receptor subtypes may be classified according to their related messenger systems. For example, V_2 receptors are activated by way of the adenylate cyclase pathway, a cascade that results in the expression of AQP-2 channels and water reabsorption (antidiuresis) and retention (Figure 3) (Ferguson et al., 2003; Knepper, 1997; Verbalis, 2003). Activation of V_2 receptors also stimulates the expression of epithelial sodium channels (ENaCs), which are primarily located in the distal nephron. The upregulation of ENaCs increases renal sodium reabsorption (Schild, 2004). V_2 receptors and their antagonists play a particularly important role in the pathophysiology of hyponatremia and its therapeutic management.

V_{1A} receptors, found on vascular smooth-muscle cells and cardiac muscle cells (Holmes, Landry, & Granton, 2003), function through the phosphoinositol pathway and increase intracellular calcium, resulting in vasoconstriction and an increased force of cardiac muscle contractility (positive inotropy). Furthermore, continued stimulation of V_{1A} receptors has been theorized to stimulate protein synthesis, leading to vascular and myocardial hypertrophy (Goldsmith & Gheorghiade, 2005; Nakamura, Haneda, Osaki, Miyata, & Kikuchi, 2000). Activated through the phosphoinositol pathway, V_{1B} (also known as V_3) receptors are located within the anterior pituitary where they are linked to the release of adrenocorticotropic hormone (Thibonnier, Conarty, Preston, Wilkins, Berti-Mattera, & Mattera, 1998).

Pathophysiology of water imbalance: AVP dysregulation

Abnormal AVP secretion may result in excess activation of V_2 receptors and AQP-2 channels. This oversecretion of AVP often is caused by conditions seen in the critical care unit, in the hospital, and in long-term care settings,

Table 2 Laboratory values

Laboratory value	Normal range	Laboratory values commonly seen in hyponatremia	Laboratory values commonly seen in SIADH
Sodium (serum)	135–146 mEq/L	<135 mEq/L (Verbalis, Ghali, Gross, Long, & Smith, 2005b)	<135 mEq/L (Verbalis et al., 2005b)
Osmolality (serum)	278–305 mOsm/kg		<275 mOsm/kg H_2O
Sodium (urine)	40–220 mEq/24 h (Boh, 2001)		>40 mEq/L/24 h (with urine sodium excretion rate equal to sodium intake) (Singer & Brenner, 2005)
Osmolality (urine)	50–1200 mOsm/kg		>100 mOsm/kg H_2O
AVP	≤2.2 pg/mL with serum osmolality <285 mOsm/kg; 2.2–8.5 pg/mL with serum osmolality >290 mOsm/kg		Inappropriately elevated relative to plasma osmolality

Note. Adapted with permission from Beers and Berkow (1999), and from Verbalis (2003) with permission from Elsevier.

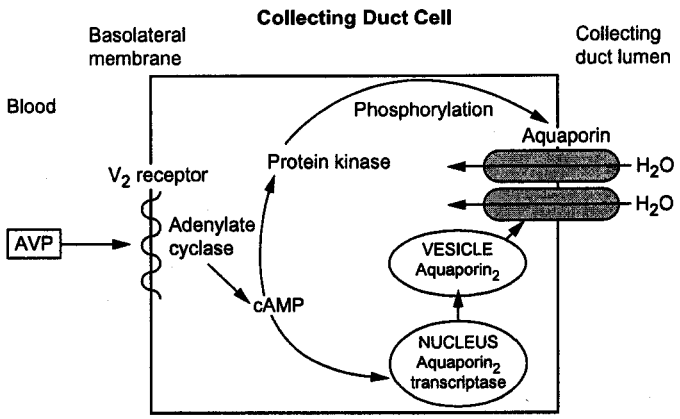

Figure 3 Effects of AVP on the renal collecting duct cell.
Note. Adapted with permission from Ferguson et al. (2003).

including those patients with central nervous system (CNS) disorders, malignancies, and inflammatory lung diseases. Oversecretion of AVP as a characteristic of these conditions can lead to SIADH (Table 3) (Miller, 2001). In SIADH, impaired free-water excretion from the kidneys increases TBW, resulting in hypoosmolality and hyponatremia. However, in most cases, even with the plasma hypoosmolality in SIADH, AVP secretion is not suppressed. Additionally, 10%–20% of cases of clinical SIADH do not have elevated plasma AVP levels (Wong & Verbalis, 2002). A careful evaluation of the cause of hyponatremia may lead a clinician to identify an underlying disorder. In some cases, treating the underlying disorder may often resolve the hyponatremic condition simultaneously (Wong & Verbalis). Frequently, elderly patients with reduced TBW and diminished renal blood flow, as well as patients on mechanical ventilation, postoperative patients, and patients with acquired immune deficiency syndrome (AIDS), are at risk for oversecretion of AVP and the development of SIADH (Miller).

Risk factors for hyponatremia

One 3-month study of geriatric patients (≥65 years; N = 172) in posthospital rehabilitation evaluated the prevalence of hyponatremia and specifically SIADH (Anpalahan, 2001). Serum sodium levels of <135 mEq/L were found in 25% of the patients studied, with only four study subjects experiencing symptoms. Of the hyponatremic group (symptomatic and asymptomatic), 51% had a medical history compatible with chronic, idiopathic SIADH (Anpalahan). Another study of dysnatremias in subpopulations (males, females, and various age groups) reported that age but not gender was found to be a strong independent risk factor for the development of hyponatremia (serum sodium <136 mEq/L). Results showed that hyponatremia was a common and generally mild condition in subjects >60 years of age in both acute hospital and ambulatory care facilities (Hawkins, 2003).

As a result of the normal aging process, the elderly may be at increased risk for the development of hyponatremia. Age-related changes in salt and water balance were identified in one study to be multifactorial and included impaired thirst, decreased GFR, changes in many hormone levels (including AVP), decreased ability to concentrate urine, and reduced ability to excrete a water load and electrolytes (Luckey & Parsa, 2003). Additionally, many prescribed medications or over-the-counter drugs may adversely affect AVP secretion in geriatric patients and lead to dysnatremias (Tareen, Martins, Nagami, Levine, & Norris, 2005). Drugs known to *enhance* AVP secretion include nicotine, high-dose morphine, epinephrine, and cyclophosphamide. Agents known to *reduce* AVP secretion include alcohol, low-dose morphine, clonidine, glucocorticoids, haloperidol, cisplatinum, and carbamazepine. Additionally, in the elderly, some drugs (e.g., tolbutamide, chlorpropamide, and nonsteroidal anti-inflammatory drugs) that interact with AVP have been found to increase renal tubular responsiveness (possibly causing antidiuresis), while other drugs (e.g., lithium, colchicine, demeclocycline, glyburide, loop diuretics, vinblastine, methoxyflurane) can diminish renal tubular responsiveness (possibly causing diuresis). These are reasons to be extremely cautious and consider that rapid change in extracellular water content may impose risks (e.g., angina, hypertension, and heart failure) (Jackson, 2001; Tareen et al.).

Table 3 Causes of syndrome of inappropriate antidiuretic hormone (SIADH)[a]

Central nervous system disorders
Vascular disease (thrombosis, embolism, hemorrhage, vasculitis)
Trauma (subdural hematoma, subarachnoid or intracranial hemorrhage)
Tumor
Hydrocephalus
Infection (meningitis, encephalitis, brain abscess)
Acute intermittent porphyria
Lupus erythematosus
Postoperative transsphenoidal hypophysectomy
Schizophrenia
Neoplasms with ectopic hormone production
Small-cell lung carcinoma
Pharyngeal carcinoma
Pancreatic carcinoma
Thymoma
Lymphoma, Hodgkin's disease, reticulum cell sarcoma
Bladder cancer
Pulmonary disease
Pneumonia
Lung abscess
Bronchiectasis
Tuberculosis
Drugs
Antipsychotics
Antidepressants (tricyclics, selective SSRIs)
Anticonvulsants
Narcotics
Hallucinogens
ACE inhibitors
Oxytocin
ADH analogs (desmopressin, lysine vasopressin)
Sulfonylureas
Clofibrate
Other
Positive pressure ventilation
AIDS
Idiopathic SIADH of the elderly

Note. ACE, angiotensin-converting enzyme; SSRIs, selective serotonin reuptake inhibitors; ADH, antidiuretic hormone.
[a]Adapted from Miller (2001) with permission from Elsevier.

Clinical consequences of hyponatremia

The symptoms of hyponatremia usually begin to appear when the serum sodium concentration falls below 125 mEq/L (Verbalis, 2003). Symptoms worsen as the sodium deficit and the rate of sodium decline increases (Arieff, 1988; Freda et al., 2004). Initial signs and symptoms may include headache, nausea, and vomiting. In later stages, as hyponatremic encephalopathy and cerebral edema develop, signs and symptoms may progress to hallucinations, lethargy, weakness, bradycardia, respiratory depression, seizures, coma, and death (Arieff). Because hyponatremia may be a secondary condition caused by an underlying disease process or because symptoms of hyponatremia may be nonspecific, other conditions (e.g., tumors, CNS disorders, pulmonary disease, endocrine disorders, or diuretic use) must first be ruled out (Verbalis; Wong & Verbalis, 2002).

Acute severe hyponatremia

With an onset of <48 h, acute severe hyponatremia is considered a medical emergency and has been associated with permanent brain damage and death. The pathophysiology of acute hyponatremia involves the loss of sodium from the ECF, creating an osmotic pressure gradient across cell membranes that tends to attract water from the extracellular space (at a low solute concentration) to the intracellular space (at a high solute concentration), resulting in intracellular edema or swelling (Adrogue & Madias, 2000). This swelling is particularly injurious to brain cells because the cranium limits the ability of the brain tissue to expand in response (Adrogue & Madias).

If acute hyponatremia is untreated, the risk of morbidity or mortality may increase (Adrogue, 2005). In a multivariate analysis of 168 hospitalized patients with hyponatremia, investigators reported that the predictors of short-term mortality included hypoxia, sepsis, and the presence of hyponatremic symptomatology (Nzerue, Baffoe-Bonnie, You, Falana, & Dai, 2003). Another study examined subjects who developed postoperative encephalopathy (Ayus, Wheeler, & Arieff, 1992). In this study, the risk of death or permanent brain damage was found to be 25 times higher in the premenopausal female subjects than in men or postmenopausal subjects. Researchers hypothesized that the physical characteristics of older men and women (cerebral atrophy seen with aging) allowed the brain to adapt to osmotic changes and edema compared with younger women. Additionally, men compared with women were found in this study to experience less severe symptomatology with the similarly diminished serum sodium levels. As a result, 90% of women died before hyponatremia was diagnosed, suggesting that, with hyponatremia, clinicians may need to identify different clinical presentations for men and women and that timely diagnosis and treatment of hyponatremia is imperative (Ayus et al.).

Chronic hyponatremia

With an onset of >48 h, chronic symptomatic hyponatremia is associated with adverse outcomes, including permanent neurological injury and death (Ayus & Arieff, 1999). During the course of chronic hyponatremia, the brain adapts to serum hypoosmolality and brain edema by

expelling organic osmolytes and electrolytes through the blood–brain barrier. Because osmolytes readapt slowly (5–7 days) to the hyperosmolar state, the patient is at risk for the development of ODS if chronic hyponatremia is corrected too rapidly. ODS is a disorder involving the destruction of the myelin sheath covering the axons in the brainstem (Laureno & Karp, 1997; Norenberg, Leslie, & Robertson, 1982; Sterns et al., 1994; Verbalis, 1993). When the pathogenesis of ODS was investigated retrospectively in 12 cases, a direct association was found between the rapid rise in serum sodium and ODS in patients with hyponatremia (Norenberg et al., 1982). Subsequent studies in patients with chronic hyponatremia strongly linked rapid correction of serum sodium with ODS (Laureno & Karp; Norenberg et al.; Sterns et al.). Therefore, if chronic hyponatremia is corrected too rapidly, complications such as ODS may result.

Hyponatremia in hospitalized patients

Hyponatremia in hospitalized patients may be associated not only with disease states (e.g., SIADH, CHF) but also with medical procedures, surgery, and medication use. In a study of hospital patients with severe hyponatremia (serum sodium $\leq$120 mEq/L), 61% had chest infections, 44% were on diuretics, 28% had CHF, 28% were postoperative, 19% had carcinoma, and 9% were on selective serotonin reuptake inhibitors (SSRIs) (Crook, Velaythar, Moran, & Griffiths, 1999). Nurse practitioners and other clinicians must be alert to the risks of hyponatremia in hospitalized patients and recognize the varied diseases and conditions associated with this disorder.

Heart failure and cirrhosis of the liver with ascites

Additionally, patients with edema-producing disorders such as CHF or cirrhosis of the liver with ascites experience decreased GFR from decreased blood volume/pressure, which can lead to elevated plasma AVP levels, edema, and hypervolemic hyponatremia (Wong & Verbalis, 2002). Patients with CHF often develop increased AVP release as part of a compensatory mechanism by which the body attempts to counteract deteriorating cardiac function and reduced effective circulating blood volume. However, increasing fluid volume via IV infusions makes it more difficult for the heart to pump blood efficiently, which can exacerbate CHF and result in higher AVP plasma levels and hyponatremia (Chatterjee, 2005; Oren, 2005).

A study of patients (N = 4031) hospitalized with heart failure showed that hyponatremia was among other predictors including age, lower systolic blood pressure (BP), higher respiratory rate, higher BUN, and comorbid conditions (e.g., cerebrovascular disease, chronic obstructive pulmonary disease [COPD]) of an increase in both 30-day and 1-year mortality (Lee et al., 2003; Oren, 2005). Additionally, treatment with diuretics to reduce fluid retention in patients with CHF may further complicate sodium and water balance. Patients with CHF, especially female and geriatric patients with low body mass, are at increased risk for diuretic-induced hyponatremia (Oren).

In patients with cirrhosis (N = 191 patient admissions), a study found that hyponatremia was present in approximately 30% of patients and was associated with chronic diuretic use, peritoneal bacterial infection, ascites, variceal bleeding, and renal failure (Borroni, Maggi, Sangiovanni, Cazzaniga, & Salerno, 2000). Inpatient mortality was three times higher for cirrhotic patients with hyponatremia than for those with normal serum sodium levels upon admission (Borroni et al.). For patients hospitalized with cirrhosis, serum sodium levels should be monitored frequently (Borroni et al.).

Syndrome of inappropriate antidiuretic hormone

The most common cause of euvolemic hyponatremia is SIADH. This condition is characterized not only by hyponatremia but also by decreased serum osmolality (<275 mOsm/kg H_2O), elevated urine sodium, concentrated urine, and normal TBW (Bartter & Schwartz, 1967; Beigel, Shiff, Luckman, & Dessau, 2005; Verbalis, 2003). Three factors explain the changes in sodium excretion seen in SIADH: (a) decreased aldosterone secretion secondary to increased ECF volume, (b) increased filtered sodium as a result of an increased GFR, and (c) suppressed reabsorption of sodium in the proximal tubules (Bartter & Schwartz). SIADH is common in the intensive care unit (ICU) as reported in a study of critical care patients (DeVita, Gardenswartz, Konecky, & Zabetakis, 1990). This 3-month retrospective study evaluating patients with hyponatremia (serum sodium $\leq$134 mEq/L) who were admitted to the ICU (98 admissions) showed that 29.6% of these patients had hyponatremia. The admitting diagnoses of the study subjects varied and included cerebral aneurysm, pneumonia (respiratory decompensation), COPD, pneumothorax, CHF, pericardial effusion, postthoracotomy, and cardiopulmonary arrest. Symptoms consistent with SIADH were observed in 10 of the 29 hyponatremic patients, suggesting that SIADH is a common disorder in critically ill patients (DeVita et al., 1990).

Pulmonary disorders

In pulmonary disorders, both low blood oxygenation and high blood carbon dioxide levels trigger an elevation of plasma AVP (Wong & Verbalis, 2002). Mechanical ventilation decreases pulmonary blood volume and left atrial pressure, which introduces potential hazards to the care of

critically ill patients (Adrogue, 2005). Continuous positive pressure and positive end-expiratory pressure ventilation may activate carotid baroreceptors and stimulate AVP release. Maintaining patients on pulmonary ventilation may cause or worsen SIADH as a result of elevations in AVP secretion. Close monitoring of serum electrolytes in these patients is recommended (Wong & Verbalis).

Plasma AVP levels have been shown to be elevated and urinary excretion of free water reduced in patients with COPD. Hypoxemia, edema, and hypercapnia associated with COPD were thought to be the effectors stimulating peripheral chemoreceptors or baroreceptors and resulting in elevated plasma AVP levels (Wong & Verbalis, 2002). Other pulmonary disorders often associated with SIADH include tuberculosis, aspergillosis, pneumonia, and empyema. These pulmonary disorders are seen radiographically as increased infiltrates or fluid levels and, clinically, these patients present with severe dyspnea (Wong & Verbalis).

CNS disorders

Diverse CNS disorders that decrease inhibitory input and affect the pathways from the brainstem to the hypothalamus may cause hypersecretion of AVP, resulting in an increased risk for developing SIADH (Wong & Verbalis, 2002). Brain injury from trauma, subarachnoid hemorrhage, or pituitary stalk distortion or compression (e.g., by tumor or cyst or surgery in the pituitary region) is frequently associated with hyponatremia (Beigel et al., 2005; Rabinstein & Wijdicks, 2003).

Cerebral salt-wasting syndrome versus the SIADH

Reported in 21%–39% of patients following transsphenoidal surgery of the pituitary region (Cole, Gottfried, Liu, & Couldwell, 2004; Olson, Rubino, Gumowski, & Oldfield, 1995; Wei et al., 2003), hyponatremia is thought to reflect increased AVP release caused by surgical stretching or compression of the pituitary stalk or posterior pituitary region or from the development of cerebral salt-wasting syndrome (CSWS), a poorly understood disorder of accelerated renal salt excretion and volume depletion following brain injury (Casulari et al., 2003; Dickerson, 2002; Olson et al.; Vacca, 2005). For neurosurgical patients, examining ECF volume differentiates CSWS (volume depletion) from SIADH (euvolemic or slightly hypervolemic) (Table 4) (Cole et al.; Harrigan, 2001).

Disorders of mental health

Self-induced water intoxication (polydipsia) combined with impaired free-water excretion may result in hyponatremia in patients with psychosis (Tanneau et al., 1994).

Table 4 Comparison of clinical findings and treatment in CSWS versus SIADH[a]

Clinical entity	CSWS	SIADH
Serum sodium	Hyponatremia	Hyponatremia
ECF	Decreased	Normal or expanded
Sodium balance	Negative	Variable
Fluid balance	Negative	Positive or at equilibrium
CVP/PCWP/EDVI	Decreased	Normal or increased
Body weight	Decreased	Increased
Serum osmolality	Increased or normal	Decreased
Urine osmolality	Increased	Increased
Urine sodium	Increased	Increased
BUN/creatinine ratio	Increased	Decreased or no change
Serum potassium	Increased or no change	Decreased or no change
Hematocrit	Increased	Normal
Treatment goal (Cole et al., 2004)	Salt and fluid replacement	Fluid restriction

Note. ECF, extracellular fluid; CVP, central venous pressure; EDVI, end-diastolic volume index; PCWP, pulmonary capillary wedge pressure.
[a]Adapted from Harrigan (2001) with permission from Elsevier.

However, other causes of hyponatremia are also evident in psychiatric patients in long-term care institutions. In a study of 1905 psychiatric inpatient cases, 3.4% had hyponatremia (serum sodium <129 mEq/L) (Siegler, Tamres, Berlin, Allen-Taylor, & Strom, 1995). In this study, causes of hyponatremia were reported to include use of fluoxetine (adjusted odds ratio 21.4), diuretic use (8.2), use of tricyclic antidepressants (4.9), and use of calcium antagonists (4.0) (Siegler et al.).

Other causes of hyponatremia

Other causes of hyponatremia include acute head injury (incidence of 4.5%–34%) (Ke et al., 2002), which is a frequent complication commonly seen 2–3 days after presentation (Rabinstein & Wijdicks, 2003). Hyponatremia following head injury may be iatrogenically caused (e.g., as a result of inadequate tonicity of IV fluids). More common, however, are the two main disorders associated with noniatrogenic causes of hyponatremia—SIADH and CSWS (Donati-Genet, Dubuis, Girardin, & Rimensberger, 2001; Rabinstein & Wijdicks). Hyponatremia has also been reported in at least 4% of patients after undergoing general surgery, often because of overhydration with hypotonic IV solutions or intraoperative irrigation fluids (Chung, Kluge, Schrier, & Anderson, 1986). For example, patients who undergo transurethral resection of the prostate (TURP) for benign prostatic hyperplasia often develop hyponatremia (TURP syndrome) as a consequence of irrigation of the

operative field with large volumes of sodium-free solutions that contain glycine, sorbitol, mannitol, or sterile water (Issa, Young, Bullock, Bouet, & Petros, 2004).

Hypothyroidism is commonly associated with hyponatremia (Baajafer, Hammami, & Mohamed, 1999; Nakano, Higa, Ishikawa, Yamazaki, & Yamamuro, 2000). Although SIADH has been associated in the literature with hypothyroidism, the underlying mechanisms are unknown. Hyponatremia has been reported in 38% of patients ($N = 167$) hospitalized with AIDS or AIDS-related complex, either as a result of gastrointestinal fluid loss (e.g., vomiting or diarrhea) or SIADH (Tang, Kaptein, Feinstein, & Massry, 1993).

Rather than causing the excessive release of AVP from the pituitary, small-cell lung carcinoma has been found to ectopically produce antidiuretic hormone (Bartter & Schwartz, 1967; George, Capen, & Phillips, 1972). Additionally, in an 11-month study of patients ($N = 106$) with cancer (including lung cancer [18%], breast cancer [16%], head and neck cancer [15%], gastrointestinal cancer [10%], and gynecological neoplasms [9%]) who required hospitalization, the incidence of hyponatremia was 3.7 per 100 hospitalizations. Hyponatremia was most commonly attributed to electrolyte depletion from gastrointestinal or renal losses, diuretic use, or SIADH (Berghmans, Paesmans, & Body, 1999).

Medications that may induce hyponatremia

Hyponatremia has been linked to the use of numerous drugs. Thiazide diuretics stimulate fluid loss, which causes a compensatory increase in AVP secretion and prevents the reabsorption of sodium by the distal tubules, resulting in increased urinary sodium loss. Loop diuretics produce the same effect, but to a lesser extent (Greenberg, 2000). Risk factors for hyponatremia with diuretic use include patient age (every increase of 10 years of age is associated with a twofold increase in risk), body weight (for every 5 kg increase in body weight, there is a 27% decrease in risk), and serum potassium level (for every 0.84 mmol/L increase in serum potassium level, there is a 63% decreased risk) (Chow, Szeto, Wong, Leung, & Li, 2003). Hyponatremia has also been associated with a number of SSRIs and serotonin and norepinephrine reuptake inhibitors, including fluoxetine, citalopram, venlafaxine, sertraline, and paroxetine, especially during the first few weeks of treatment (Alderman, 2002; Ertel & Nesbit, 2002; Fabian et al., 2004; Matsumoto, 2005; Movig, Leufkens, Lenderink, & Egberts, 2002; Woo & Smythe, 1997). Anticonvulsants such as levetiracetam, carbamazepine, and oxcarbazepine have been reported to increase the risk for hyponatremia by increasing either the release of AVP or the sensitivity of AVP receptors (Nasrallah & Silver, 2005; Ryan, Adams, & Larive, 2001). AVP secretion and hyponatremia have also been reported with cigarette smoking and, in a recent case report, with the use of nicotine replacement therapy (Finch, Andrus, & Curry, 2004). Case reports or retrospective studies have described hyponatremia in association with several other drugs, including the proton-pump inhibitor esomeprazole (Mennecier, Ceppa, Gidenne, & Vergeau, 2005), the synthetic AVP analog desmopressin (Callreus, Ekman, & Andersen, 2005), the amphetamine derivative MDMA (ecstasy) (Rukskul, 2005), and the antiarrhythmic drug amiodarone (Patel & Kasiar, 2002).

Assessment and treatment of hyponatremia

Patient assessment for hyponatremia should include a targeted history, examination for pertinent neurological signs and symptoms, laboratory tests, assessment of ECF volume status, a review of recent and current IV fluid orders, and a review of all medications (Figure 4) (Freda et al., 2004; Goh, 2004; Koay & Walmsley, 1996). In addition, a determination of whether the patient's presentation is acute (duration of <48 h) or chronic (duration of >48 h) should be made (Freda et al.; Goh; Verbalis, 2003). Assessment of ECF volume (euvolemia, hypervolemia, or hypovolemia) relies primarily on a targeted history and physical examination, including evaluation of the patient's history for diarrhea, vomiting, excessive thirst, and/or polyuria; nursing records for daily weight and cumulative fluid intake and output; and a physical exam for orthostasis, neck vein distention, peripheral or pitting edema, and/or ascites (Beers & Berkow, 1999; Freda et al.).

In a study evaluating ECF volume in 58 nonedematous patients with serum sodium <130 mEq/L, clinical assessment correctly identified only 47% of hypovolemic patients and 48% of normovolemic patients (Chung, Kluge, Schrier, & Anderson, 1987). Measures of total body resistance using a noninvasive procedure called bioelectrical impedance analysis provide an estimate of hydration status of patients and can also provide a definitive guideline for the management of adequate fluid balance (Allison, Ray Lewis, Liedtke, Buchmeyer, & Frank, 2005). If available, ultrasound assessment of tissue hydration can also be effective in monitoring total body hydration (Sarvazyan, Tatarinov, & Sarvazyan, 2005), and a spot urine determination can clearly separate hypovolemic patients from their normovolemic counterparts (Chung et al., 1987).

Treatment of acute and chronic hyponatremia

Conventional therapies for the treatment of hyponatremia include fluid restriction and the administration of hypertonic saline and pharmacological agents such as

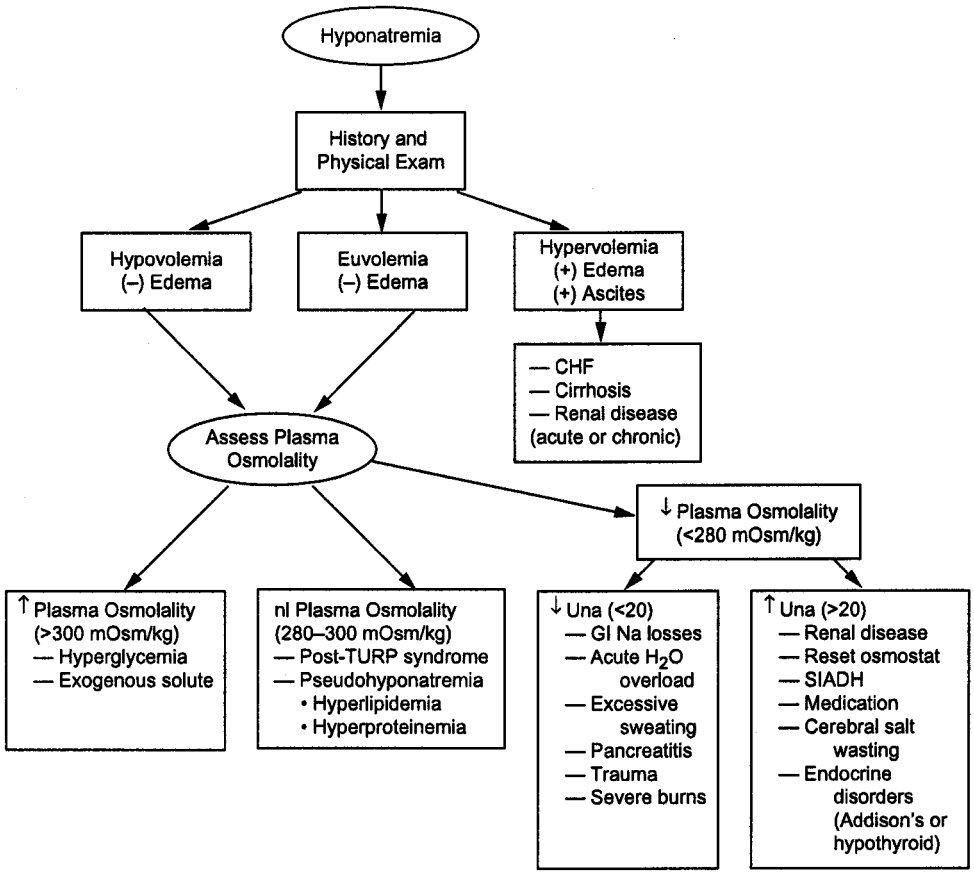

Figure 4 Assessment of hyponatremia.
Note. GI, gastrointestinal; Una, urinary sodium; TURP, transurethral resection of the prostate; SIADH, syndrome of inappropriate diuretic hormone; CHF, congestive heart failure. Adapted with permission from Koay and Walmsley (1996).

demeclocycline, lithium carbonate, and urea (Adrogue, 2005; Goh, 2004; Miller, Linas, & Schrier, 1980; Nguyen & Kurtz, 2005; Schrier, Berl, & Anderson, 1979; Verbalis, 2003). Many of these treatments are not Food and Drug Administration (FDA) approved for the treatment of hyponatremia and may be limited by variable efficacy, slow onset of action, patient compliance issues, and toxicities (Goldsmith & Gheorghiade, 2005; Wong & Verbalis, 2002).

Fluid restriction of less than 800 mL/day raises serum sodium by only 1–2 mEq/L per day, and patient compliance with this treatment is difficult to maintain. Additionally, patients receiving IV treatments (e.g., antibiotics, chemotherapy, or parenteral feedings) for other conditions may be unable to comply with fluid restriction. Use of hypertonic saline requires complex calculations of sodium requirements and rate of replacement.

Conventional pharmacological agents take several days to achieve maximal effect and can sometimes result in significant toxicities. Demeclocycline, a tetracycline derivative used by some clinicians to assist with the management of hyponatremia, inhibits the antidiuretic effect of AVP on the renal tubules and increases the excretion of solute-free urine but is associated with a slow onset of action and significant risk for nephrotoxicity (Miller et al., 1980). Lithium carbonate is also not appropriate for acute settings and is associated with neurological side effects, cardiotoxicity, and gastrointestinal disturbances. Although effective, urea has poor palatability and is contraindicated in cases of impaired renal function, intracranial bleeding, or liver failure (Goldsmith, 2005; Wong & Verbalis, 2002).

For patients with severe acute symptomatic hyponatremia, hypertonic saline (3% NaCl) is used for the correction of the sodium deficit and may be combined with the

diuretic furosemide (Adrogue & Madias, 2000; Goh, 2004; Verbalis, 2003). Furosemide inhibits sodium and chloride reabsorption in the proximal renal tubules in the loop of Henle and thus increases the volume of tubular fluid, leading to increased excretion of solute-free water in the distal tubules (Schrier, Lehman, Zacherle, & Earley, 1973.)

For patients with chronic asymptomatic hyponatremia (and with asymptomatic hyponatremia of indeterminate origin), water restriction is the first line of treatment. However, patients find water restriction difficult to tolerate, and this can lead to poor patient compliance (Adrogue, 2005; Goh, 2004). Hypertonic saline may be used as the initial treatment of symptomatic chronic hyponatremia. Then, if either symptoms resolve or there is a 10% increase of serum sodium levels, water restriction is recommended (Thurman, Halterman, & Berl, 2003). Because of the risk for neurological injury from ODS, sodium correction using hypertonic saline should be made at a rate of not more than 1–2 mEq/L per h and not more than 12 mEq/L per 24 h or 18 mEq/L over the first 48 h (Laureno & Karp, 1997; Sterns et al., 1994).

Correction formulae

The following formulae may assist NPs in treating patients with normal or hypertonic saline (Decaux, Musch, & Sterns, 2000; Verbalis, 2003). The estimated change in serum sodium levels using 0.9% or 3% sodium chloride (NaCl) IV infusion may be calculated as follows (Adrogue & Madias, 1997; Kraft, Btaiche, Sacks, & Kudsk, 2005):

1. First, calculate the estimated TBW—men: TBW = 0.6 L/kg × body weight (kg); women: TBW = 0.5 L/kg × body weight (kg).

2. Next, calculate the change in serum sodium concentration (Adrogue & Madias, 1997; Kraft et al., 2005):

$$\text{Change in serum sodium concentration} = \frac{Na_{infusate} - Na_{patient}}{TBW + 1}$$

$Na_{infusate}$ = 513 mEq/L (sodium concentration after 1 L of 3% NaCl IV infusion) or 154 mEq/L (sodium concentration after 1 L 0.9% NaCl IV infusion); $Na_{patient}$ = patient's serum sodium concentration (mEq/L).

Reasonable correction parameters consist of a maximal rate of correction of serum sodium in the range of 1–2 mEq/L per h as long as the total magnitude of correction does not exceed 25 mEq/L over the first 48 h. Regardless of the initial rate of correction chosen, acute treatment should be interrupted if any of three endpoints is reached: (a) the patient's symptoms are abolished, (b) a safe serum sodium (generally ≥120 mEq/L) is achieved, or (c) a total magnitude of correction of 20 mEq/L is achieved (Verbalis, 2003).

AVP receptor antagonists: A new class of therapeutic agents for the treatment of hyponatremia

The AVP receptor antagonists lixivaptan and tolvaptan are currently in clinical development for the treatment of hyponatremia, in addition to other indications. IV conivaptan hydrochloride has been FDA approved for the treatment of euvolemic hyponatremia in hospitalized patients. Lixivaptan and tolvaptan inhibit the V_2 receptor only, while conivaptan blocks the effects of both V_{1A} and V_2 receptors. Several studies have found that AVP receptor antagonists stimulate free-water excretion and improve serum sodium concentration in patients with hyponatremia including those with SIADH (Gheorghiade, Konstam, Udelson, Ouyang, & Orlandi, 2002; Gheorghiade, Zimmer, Czerwiec, Ouyang, & Orlandi, 2005b; Gheorghiade et al., 2004, 2005a; Palm, Reimann, & Gross, 2001; Verbalis, Ghali, Gross, Long, & Smith, 2005a). Although studies with lixivaptan have shown that V_2 antagonism may be beneficial in patients with hyponatremia and liver cirrhosis with ascites (Gerbes et al., 2003; Guyader, Patat, Ellis-Grosse, & Orczyk, 2002), conivaptan and tolvaptan have not been studied extensively in this setting. Note also that AVP receptor antagonists are not considered appropriate for the treatment of hypovolemic hyponatremia because of the risk of further fluid depletion (Wong & Verbalis, 2001). The following are some of the pertinent clinical data on this new class of agents, the AVP receptor antagonists.

Conivaptan

IV conivaptan hydrochloride (Vaprisol®, Astellas Pharma US, Inc., Deerfield, IL) is a dual V_{1A}/V_2 receptor antagonist that has been approved for the treatment of euvolemic hyponatremia in hospitalized patients ("Vaprisol PI," 2006). (Vaprisol has not been approved for use in patients with hypovolemia or patients with CHF.) The principal pharmacodynamic effect of conivaptan is the blockade of V_2 receptors in the renal collecting ducts, thus reducing water reabsorption, promoting aquaresis, decreasing urine osmolality, and increasing plasma sodium concentration ("Vaprisol PI").

In an open-label safety and efficacy study, the pharmacokinetics of conivaptan was determined in patients (51–89 years of age) with euvolemic or hypervolemic hyponatremia. Subjects received an initial IV infusion of conivaptan (20 mg infused over 30 min) followed by an infusion of 40 mg/day for 4 days. The C_{max} of 781 ng/mL was reached at the conclusion of the loading dose, and the median plasma conivaptan concentration at the end of the infusion was 228 ng/mL. The elimination half-life

after termination of the infusion was approximately 9 h, and the rate of clearance was 9.5 L/h ("Vaprisol PI," 2006).

The efficacy of conivaptan for the treatment of hyponatremia has been evaluated in several double-blind placebo-controlled clinical trials. The effects of conivaptan were examined at IV doses of 40 or 80 mg/day via continuous infusion on serum sodium concentration in one IV and two oral studies (Verbalis et al., 2005a). In all three studies, patients had euvolemic or hypervolemic hyponatremia with mean baseline serum sodium values of 124–126 mEq/L. In the IV study, patients ($N = 84$) who received conivaptan reported mean improvements in serum sodium of 6.8 mEq/L with the 40-mg dose ($p = .0001$), and 9.0 mEq/L with the 80-mg dose ($p = .0001$). After 4 days, patients administered placebo exhibited a mean improvement in serum sodium of 2.0 mEq/L (Verbalis et al., 2005a). In other analyses, IV conivaptan (20-mg bolus followed by a 40 or an 80 mg/day infusion for 4 days) investigators reported improved mean change in serum sodium area under the curve to day 4 ($p < .001$ compared with placebo) and increased extracellular water content (aquaresis) on day 1 ($p < .05$ compared with placebo) in patients with hyponatremia (Verbalis, Bisaha, & Smith, 2004a, 2004b). The only reported adverse event that appears significant for conivaptan IV is an inflammatory response at the infusion site ("Vaprisol PI," 2006).

Lixivaptan

The V_2 receptor antagonist lixivaptan has also been evaluated in clinical trials. Lixivaptan was examined in a study of 60 patients with cirrhosis and dilutional hyponatremia (Gerbes et al., 2003). The primary endpoint was normalization ($\geq$136 mEq/L) of serum sodium, which was achieved by 27% and 50% of patients who received oral lixivaptan at doses of 100 ($p < .05$) and 200 mg/day ($p < .001$), respectively, over 7 days or until the primary endpoint was achieved. The mean time to normalization of serum sodium was 4.8 days (200-mg lixivaptan group) and 5.7 days (100-mg lixivaptan group). In a study of 44 patients with SIADH, cirrhosis, or CHF, patients were randomized to treatment with placebo or one of three lixivaptan doses (25, 125, or 250 mg twice daily) (Wong, Blei, Blendis, & Thuluvath, 2003). Lixivaptan produced a dose-related increase in free-water clearance, serum sodium concentration, and serum osmolality.

Tolvaptan

Tolvaptan has also been shown to increase urine output and serum sodium concentration and to reduce edema following oral administration of 30–90 mg/day in patients with chronic heart failure, volume overload, and hyponatremia (Gheorghiade et al., 2002, 2003a, 2005a, 2005b). The effects of tolvaptan were investigated in the Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure study, a large multicenter trial examining patients ($N = 320$) who demonstrated at least two signs of heart failure and experienced New York Heart Association Class III/IV heart failure at screening and left ventricular ejection fraction of <40% during the previous 12 months (Gheorghiade et al., 2003b). In the hospitalized subjects, median weight loss at approximately 24 h was −1.8 kg (30 mg), −2.1 kg (60 mg), and −2.8 kg (80 mg) versus 0.6 kg for placebo ($p \leq .008$ for all doses versus placebo). In the outpatient phase of the study, the primary endpoint of worsening heart failure was indistinguishable between tolvaptan- and placebo-treated subjects ($p = .88$); however, 60-day mortality in patients with renal dysfunction and systemic congestion was reduced in the tolvaptan group versus placebo ($p = .18$) (Gheorghiade et al., 2004). The increase in serum sodium during hospitalization for subjects with CHF and hyponatremia was a predictor of an improved mortality rate at 60 days ($p < .0269$) (Gheorghiade et al., 2005b).

Case study

An attending neurologist reported admitting a 70-year-old woman to the hospital for evaluation of an altered level of consciousness and convulsions (Nakano et al., 2000). She gave a history of fatigue and sleepiness without nausea for 6 months and a 27-year history of hypertension, for which she currently takes angiotensin-converting enzyme inhibitors.

Physical examination on admission revealed a BP of 156/74, a pulse of 70 beats/min, and a stuporous state. She followed commands slowly. There was no jaundice or edema; chest and abdominal examinations were normal. Additional neurological findings were negative except for depressed Achilles reflexes bilaterally.

Laboratory values showed hyponatremia (serum sodium 103 mEq/L), low plasma osmolality (208 mOsm/L), high urine osmolality (513 mOsm/L), and urinary sodium of 51 mEq/24 h (Table 5). The patient had elevated levels of serum aspartate aminotransferase, lactic dehydrogenase, creatine phosphokinase, and thyroid-stimulating hormone, in addition to low levels of uric acid, free T3, and free T4. Antithyroglobulin and antithyroperoxidase antibodies were both positive.

Admission chest X-ray was normal and magnetic resonance imaging of the brain revealed the sella turcica normal in shape and size; however, the posterior pituitary showed a high intensity on T1-weighted imaging. Abdominal computerized tomography scanning revealed bilateral enlargement of the adrenal glands.

Table 5 Case study laboratory values on admission[a]

Plasma ADH	22.8 pg/mL
Serum TSH	16.2 μU/mL
Serum FT_3	1.3 pg/mL
Serum FT_4	0.3 ng/dL
Plasma renin activity	0.1 ng/mL/h
Plasma aldosterone	2.6 ng/dL
Serum cortisol	33.9 μg/dL
Antithyroglobulin antibody	100 U/mL
Antithyroperoxidase antibody	12.7 U/mL
Serum sodium	103 mEq/L
Serum potassium	3.6 mEq/L
Serum chloride	56 mEq/L
BUN	9 mg/dL
Creatinine	0.5 mg/dL
Uric acid	1.7 mg/dL
Aspartate aminotransferase	172 IU/L
Alanine aminotransferase	28 IU/L
Lactic dehydrogenase	1194 IU/L
Creatine phosphokinase	3312 IU/L
Plasma osmolality	208 mOsm/L
Urine osmolality	513 mOsm/L
Urine sodium	51 mEq/24 h

Note. ADH, antidiuretic hormone; FT, free triiodothyronine; TSH, thyroid-stimulating hormone.
[a]Adapted with permission (pending) from Nakano et al. (2000).

The patient's admission laboratory data appeared to indicate that the hyponatremia was associated with SIADH (high plasma AVP level with low plasma osmolality); she was also diagnosed as having primary hypothyroidism as a result of Hashimoto's thyroiditis.

Conventional treatment was begun with water restriction and sodium supplementation, and steady improvement was noted in consciousness level. After 3 weeks, serum sodium levels reached 135 mEq/L and the patient's symptoms resolved. The patient was given levothyroxine (150 μg/day).

Today, this patient would be a candidate for therapy with AVP receptor antagonists.

Conclusions

NPs are in a unique position to identify and manage patients with hyponatremia. Symptomatic hyponatremia is a medical emergency that requires prompt but careful medical management, and hyponatremia is common in institutionalized patients and in critical care settings where this disorder may be associated with substantial increases in morbidity and mortality. Identifying patients who are at risk (the key to making an early diagnosis) and recognizing the signs and symptoms of hyponatremia are of primary importance. Additionally, understanding basic renal physiology and acid/base/water balance is critical in the management of hyponatremic patients. Awareness of the limitations of conventional therapies and the availability of new treatment options for hyponatremia allows NPs to optimize patient care. A new class of drugs, the AVP receptor antagonists (or aquaretics), has been shown to be safe and effective for the treatment of patients with hyponatremia. One of these agents, IV conivaptan hydrochloride, is FDA approved for therapy of euvolemic hyponatremia in hospitalized patients.

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